

**REMARKS****Amendments**

The title is amended for correspondence with the pending claim. The amendment adds no new matter to the disclosure.

**Rejection under 35 U.S.C. § 112, second paragraph**

Claim 7 was rejected under § 112, second paragraph, as indefinite for reciting “rituximab.” The Office contends that this term is a “laboratory designation” that does not identify a distinct antibody. The Office further suggests that the rejection would be obviated by amending the claim to recite that rituximab “is a humanized [sic] anti-CD20 monoclonal antibody.” Applicant traverses the rejection.

As evidenced by the attached excerpts from the World Health Organization publication, “International Nonproprietary Names (INN) for Biological and Biotechnological Substances,” rituximab is the INN for a specific antibody substance. As the publication states, “nonproprietary names [are assigned] to medicinal substances, so that each substance would be recognized globally by a unique name.” Thus, rituximab is not an arbitrary laboratory designation, but instead is an art-recognized designation for a particular chimeric anti-CD20 antibody substance. As the present application indicates, rituximab is the active antibody substance in the FDA-approved drug product, RITUXAN®, and its properties are well-known in the art. Moreover, amending claim 7 to recite that rituximab is a chimeric anti-CD20 monoclonal antibody would merely add language describing properties that are understood in the art to be inherent to the rituximab antibody.

Applicant submits that the questioned term adequately apprises one of skill of the metes and bounds of the claim and requests that the examiner withdraw the rejection.

**Rejection under 35 U.S.C. § 103**

Claim 7 remains subject to rejection under § 103 based on Maloney *et al.* (*Blood*, 1997) in view of Press *et al.* (*Lancet*, 1995), Kaminsky *et al.* (*JCO*, 1996), and Kaminsky (U.S. Patent No. 6,287,537), further in view of Wahl *et al.* (ASCO abstract, 1998). For the reasons that follow, applicant respectfully traverses the rejection.

First, the Office has not presented evidence that establishes that the term “refractory,” as used in the claim, has the broad meaning alleged in the rejection. The question is not, as the Office appears to argue, whether the claim should recite particular language, but what one of skill at the time of the invention would have understood the language of the claim to mean. For the reasons argued at length previously, applicant maintains that the examiner has not presented evidence that demonstrates that “refractory,” a term of art in clinical oncology, would have been understood by one of skill as the equivalent of “nonresponsive,” as the Office holds.

Second, the Office cites teachings that the cited prior art does not set forth as evidence of motivation and a reasonable expectation of success. In particular, none of the cited references teaches that a radiolabeled anti-CD20 antibody would be expected to be efficacious to treat a B-cell lymphoma patient refractory to any unlabeled anti-CD20 antibody, as the Office appears to believe.

The primary reference cited by the Office, Maloney, does not discuss treatment options for non-Hodgkin’s lymphoma (NHL) patients who fail to respond to the administration of rituximab. Whether or not such patients are “refractory” to rituximab, as the Office asserts, Maloney teaches nothing more than their lack of response to the chimeric anti-CD20 antibody therapy. The reference is silent as to any other therapy that might be attempted.

The Wahl abstract does not appear to relate to the subject matter of the claim. While it describes the administration of a second course of [<sup>131</sup>I]-anti-B1 radioimmunotherapy to NHL patients, it is silent about whether any of the treated patients were refractory to prior therapy using an unlabeled antibody.

The two Kaminski references set forth details of a therapeutic regimen that combines a “pre-dosing” of unlabeled anti-B1 antibody and a therapeutic dose of the same antibody bearing

an  $^{131}\text{I}$  radiolabel. Importantly, neither reference identifies or discusses any patient that fails to respond to a therapeutic dosage of unlabeled antibody. Every patient described in the *JCO* paper and in the '537 patent was treated with the complete "pre-dosing"-plus-radiotherapy regimen. Neither reference describes a control involving the treatment of an evaluable patient with only unlabeled antibody. Furthermore, neither reference reports on any patient given a full "pre-dosing" quantity of unlabeled antibody in advance of a radiotherapeutic dose of  $[^{131}\text{I}]$ -anti-B1 by as long as the interval that the authors/applicants allowed for assessing a clinical response to radiotherapy. Thus, neither reference examines whether any patient responded or failed to respond to any effective dose of unlabeled anti-B1. Neither Kaminski reference provides evidence of motivation to treat the specific population of patients required by the claim, because neither identifies or discusses such a population.

The Office, however, believes that "Kaminsk[i] '587] teach[es] that the radiolabeled anti-CD20 is effective in those cases where the patients do not respond to non-radiolabeled anti-CD20 alone." To support this conclusion, the Office cites the '587 patent at col. 21, lines 48-54, reproduced here:

10). However, in these cases and those in which a response appeared to occur only after an RIT dose, a targeted radiation effect is also likely, especially since targeting of radioisotope was found to be so high in these cases and could result in the delivery to tumor of up to 120 cGy per tracer dose (Table 2).

50

This passage teaches that the full benefit of the regimen is observed only after radioimmunotherapy (RIT), not that any of the patients were demonstrated to be refractory to unlabeled antibody. This is particularly so inasmuch as the protocol to which the cited passage relates involves administration of unlabeled antibody with a tracer dose of radiolabel over a period of 0 to 4 weeks ('587 at col. 14, lines 5-12), followed by a therapeutic dose of radiolabeled antibody in a timeframe only described as "[a]t least one week after the last tracer-labeled dose" (col. 14, line 13). In contrast, clinical responses to the radiotherapy regimen is evaluated "4 to 6 weeks post RIT, and every two to three months thereafter" (col. 16, lines 8-9). The cited passage does not allow one of skill to conclude whether or not any of the reported patients would have failed to respond to the administration of unlabeled antibody alone.

Moreover, the logic of the Office's argument cuts against the teachings of the Kaminski references. If one of ordinary skill considered that a given patient was refractory to an unlabeled antibody, that patient would not be treated with any additional unlabeled antibody since the treatment would be expected to be without effect. Yet Kaminski teaches that "pre-dosing" with unlabeled antibody contributes to the effectiveness of the radioimmunotherapy protocol described in the references. Neither Kaminski reference provides motivation to omit part of the therapeutic protocol it sets forth.

In summary, neither Kaminski reference supplies evidence of motivation to employ the radioimmunotherapy protocol it describes, much less only a part of such a protocol, to treat any group of patients who do not respond to a course of rituximab, such as those reported in the Maloney reference, or who are refractory to rituximab. Moreover, neither reference provides any scientific basis for reasonably expecting that any such therapy would be successful. In the absence of any evidence of motivation or a reasonable expectation of success in the practice of the proposed combination, the Office has not set forth a *prima facie* case of obviousness. Accordingly, the rejection under 35 U.S.C. § 103 should be withdrawn.

### **Conclusion**

Applicant believes that this reply fully responds to the outstanding Office action. Applicant requests that the Office reconsider the outstanding rejections and indicate that the pending claim is allowable.

Should the examiner have any questions, she is invited to contact the undersigned.

Respectfully submitted,

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